REMARKS

Claims 76-86 are pending in this application.

I. THE CLAIM REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 76-86 are rejected under 35 U.S.C. § 103(a) ("Section 103(a)") as allegedly being obvious over Weichold *et al.*, International Publication No. WO 00/33654 ("Weichold *et al.*"). The Examiner alleges that Weichold *et al.* specifically named ritonavir, saquinavir, nelfinavir and indinavir and performed assays using these specific HIV protease inhibitors ("HIV-PIs"), especially ritonavir, and that based on the observations of Weichold *et al.* that ritonavir, saquinavir, nelfinavir and indinavir provided protected effects for cells, one of ordinary skill in the art would find motivation to substitute any of the other named and tested HIV-PI (saquinavir, nelfinavir and indinavir) for ritonavir in the tumor assays and have a reasonable expectation of success and predictability because all four HIV-PIs produced a similar result in prior assays. *See* Office Action, page 7, last paragraph, lines 3-12. The Examiner also alleges that it would have been obvious to try saquinavir, nelfinavir and indinavir in the ritonavir-tumor assays with a reasonable expectation of success because there is a finite number of HIV-PIs suggested by Weichold *et al.* and because all four HIV-PIs produced a similar result in prior assays. *See* Office Action, page 8, first paragraph. For the following reasons, Applicant disagrees.

The relevant case law regarding obviousness was discussed in the Amendment Under 37 C.F.R. § 1.111 ("Amendment") filed September 26, 2008 (see page 7, last paragraph to page 9, first paragraph), and is not repeated herein.

As explained in detail below, there is nothing in Weichold *et al.* that teaches or suggests the selection of the particular HIV-PI (indinavir) for the particular use (treating a tumor or blocking cell migration or invasion) at the particular dosage (1200 mg per day) recited in claims 76 and 77, out of all possible combinations of HIV-PIs (more than three dozens as described on page 25, line 3 to page 26, line 21 of Weichold *et al.*), indications (close to a dozen as described on page 23, line 22 to page 24, line 3 and page 28, lines 4-15 of Weichold *et al.*), and dosages (see broad range disclosed at page 29, lines 19-24 of Weichold *et al.*) disclosed in Weichold *et al.*

The Examiner's allegation that the four HIV protease inhibitors, ritonavir, saquinavir, nelfinavir and indinavir, produced a similar result in prior assays and that this suggests that

they work via similar mechanisms, cannot be supported by the teaching of Weichold *et al.* and is contrary to knowledge common in the art. It appears that the Examiner's allegation is based on Example XIII of Weichold *et al.* (in particular, see page 51, lines 18-21) which states that "similar" pro-cell-survival effects on peripheral blood mononuclear cells (PBMCs) were observed for saquinavir, nelfinavir, and indinavir, as for ritonavir. However, Figures 2 and 3 of Weichold *et al.* clearly show that the pro-cell-survival effects of the four HIV protease inhibitors are not all similar. For example, Figure 2 of Weichold *et al.* shows that indinavir had a significantly less effect, if any, on cell viability, as compared to the other HIV-PIs. In addition, Figure 3 of Weichold *et al.* shows that both indinavir and saquinavir, unlike ritonavir, had little or no effect on apoptosis at low concentration. Based on these observations, one of ordinary skill in the art would not presume that the four HIV-PIs "produced a similar result in prior assays." Nor is there any teaching or suggestion in Weichold *et al.* that would lead one of ordinary skill in the art to reach the Examiner's conclusion that the four HIV-PIs work via similar mechanisms.

To the contrary, it was well known in the art that these four HIV-PIs have different properties and mechanisms of action; thus, one of ordinary skill in the art would not view the disclosure of Weichold *et al.* regarding the anti-tumor effects of ritonavir as giving rise to any reasonable expectation of success in using another HIV-PI, such as indinavir, to treat cancer. As previously discussed in the Amendment filed on September 26, 2008 (see page 10), U.S. Patent No. 6,506,555 ("the '555 patent") (made of record as reference A01 in the Information Disclosure Statement filed September 15, 2005) compared the effects of ritonavir, saquinavir, indinavir and nelfinavir in an animal model known to measure cytotoxic T lymphocyte (CTL) response. The '555 patent discloses that ritonavir and saquinavir, but not indinavir and nelfinavir, inhibited footpad swelling in mice injected with LCMV (lymphocytic choriomeningitis virus) and the direct lysis *ex vivo* after systemic infection, both of which measure the intensity of CTL response (see the '555 patent, col. 8, lines 22-27 and 36-47). The '555 patent also discloses that ritonavir and saquinavir, but not indinavir and nelfinavir, inhibited "chimotrypsin-like" activity, and states that "the specific and selective inhibition of proteasome by ritonavir as well as with saquinavir would explain the modulatory effects of the antigen presentation observed in vivo" (see the '555 patent, col. 8, lines 31-34). Based on the teaching of the '555 patent, one of ordinary skill in the art would understand that ritonavir and saquinavir trigger different immune responses than indinavir and nelfinavir.

In response to Applicant's argument made in the Amendment filed on September 26, 2008, the Examiner alleges that since footpad swelling and cancer are two very different conditions, observations of the effects of the HIV-PIs on footpad swelling are not predictive of what may occur when treating cancer with the same inhibitors (see Office Action, page 7, second and third paragraphs). Based on the Examiners' logic, there is even less basis in Weichold *et al.* to support the allegation that indinavir would have the same anti-tumor effects as ritonavir, since the Examiner relies on data concerning an indication irrelevant to and contrary to the pathology of tumor (*i.e.*, survival of PBMC exposed to "stress factors" known to be involved in HIV pathogenesis; see Weichold *et al.* at page 51, lines 8-10). Applicant cited the teachings of the '555 patent to show that it was common knowledge at the time of the invention that indinavir and ritonavir have different mechanisms of action, and thus, one of ordinary skill in the art would expect these HIV-PIs to have different clinical properties, and would not expect them to behave in a similar fashion, regardless of the indication. Moreover, as discussed above, the data in Weichold *et al.* is in fact supportive of different mechanisms of action and properties.

Moreover, the Examiner's attention is directed to Weichold *et al.*, "HIV-1 protease inhibitor ritonavir modulates susceptibility to apoptosis of uninfected T cells," J Hum Virol., 1999, 2(5):261-269 ("Weichold 1999"), and Lu *et al.*, "HIV protease inhibitors restore impaired T-cell proliferative response in vivo and in vitro: a viral-suppression-independent mechanism," Blood, 2000, 96(1):250-258 ("Lu *et al.*") (made of record as references C12 and C11, respectively, in the Supplemental Information Disclosure Statement submitted concurrently herewith). Weichold 1999 discloses that ritonavir increases the viability of PBMCs from uninfected donors (see Weichold 1999, Abstract, second paragraph). In contrast, Lu *et al.* reports that indinavir and saquinavir do not affect the viability of PMBCs from uninfected donors (see Lu *et al.*, page 255, col. 1, first paragraph, lines 10-13). Together, these references show that at the time of the invention, one of ordinary skill in the art would understand that ritonavir and indinavir have different properties and that studies with ritonavir do not predict the properties of indinavir.

Additionally, the Examiner's attention is also directed to Dowell *et al.*, "Suppression of preadipocyte differentiation and promotion of adipocyte death by HIV protease inhibitors," J Biol Chem., 2000, 275(52):41325-41332 ("Dowell *et al.*") (made of record as reference C09 in the Supplemental Information Disclosure Statement submitted concurrently herewith).

Dowell *et al.* reports that nelfinavir, but not indinavir, ritonavir and saquinavir, inhibited lipid accumulation in preadipocytes induced to differentiate (see Dowell *et al.*, page 41327, col. 1, Results section, first paragraph, lines 14-17). Dowell *et al.* states that "[d]ifferential drug concentrations and drug penetrance at the site of action would be important determinants of drug effect *in vivo*" (see Dowell *et al.*, page 41332, col. 1, second paragraph, lines 6-8). Applicant submits that, based on the teaching of Dowell *et al.*, one of ordinary skill in the art would understand that properties observed for one HIV-PI does not predict properties for another HIV-PI.

Because differences in actions between ritonavir and indinavir were commonly known in the art, one of ordinary skill would not predict indinavir to act like ritonavir. Thus, the teachings relating to ritonavir in Weichold *et al.* do not give one of ordinary skill in the art any reason to expect that indinavir could be used successfully to treat cancer.

Furthermore, it was well known in the art that these HIV-PIs have different pharmacological properties, safety profiles, clinical efficacy, and resistance problems; thus, one of ordinary skill in the art would not expect the ritonavir data disclosed in Weichold *et al.* to be predictive of indinavir's usage for any indication at any dosage. The Examiner's attention is respectfully directed to Deeks *et al.*, "HIV-1 protease inhibitors. A review for clinicians," JAMA, 1997, 277(2):145-153 ("Deeks *et al.*") and Flexner C., "HIV-protease inhibitors," N Engl J Med., 1998, 338(18):1281-1292 ("Flexner") (made of record as references C08 and C10, respectively, in the Supplemental Information Disclosure Statement submitted concurrently herewith). For example, Deeks *et al.* teaches that while saquinavir, ritonavir, indinavir and nelfinavir are structurally related, each of them has different pharmacokinetic and pharmacodynamic properties (see Deeks *et al.*, page 146, col. 2, third paragraph to page 147, col. 2, first paragraph), and unique safety and tolerability profiles (see Deeks *et al.*, page 147, col. 2, second paragraph to page 148, col. 1, second paragraph), and thus, different dosing regimens (see Deeks *et al.*, Table 1 at page 148). Flexner similarly acknowledges that dosing regimens differ for these protease inhibitors due to differences in clinical pharmacological properties (see Flexner, page 1281, col. 2, last paragraph, lines 1-5) and side effects (see Flexner, page 1286, col. 2, first paragraph, lines 1-2).

As discussed above, Weichold *et al.* does not provide any reasonable expectation of success in the use of indinavir to treat a tumor or block cell migration in a human subject, since it was well known in the art that indinavir and ritonavir have different properties and

thus, anti-tumor effects by one is not predictive of anti-tumor effects by another. Moreover, Weichold *et al.* fails to provide a reasonable expectation of success in the use of indinavir to treat a tumor or block cell migration in a human subject for the additional reason that Weichold *et al.* does not disclose any data convincing of efficacy in such use. The only indinavir data disclosed in Weichold *et al.* concerns its pro-cell-survival effect on PBMCs exposed to "stress factors" known to be involved in HIV pathogenesis (see Example XIII at pages 49-51), which sheds no light on cancer treatment efficacy.

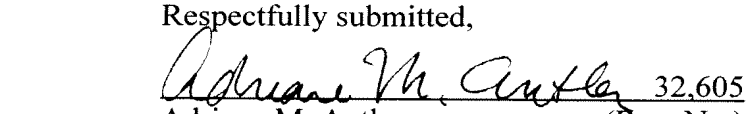
For at least the foregoing reasons, claims 76 and 77, and their dependent claims, are not obvious over Weichold *et al.* Withdrawal of the Section 103(a) rejections is respectfully requested.

CONCLUSION

Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same. If any additional fee is required for the submission of this response, please charge any such fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: June 8, 2009



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Adriane M. Antler (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

Enclosures